REMARKS

The applicants thank the examiners for consideration of applicant's response filed on July 20, 2005. In order to advance prosecution, Applicants have amended claim 18 and dependent claims 19, 20 and 28-38 and have canceled claims 21-27. Specifically, claim 18 has been amended to recite a chemically synthesized double stranded nucleic acid molecule, wherein the double stranded nucleic acid comprises a first strand and a second strand; the first strand comprises a sense region and the second strand comprises an antisense region; each strand is about 18 to about 27 nucleotides in length, about 18 to about 23 nucleotides of each strand are complementary to each other, and at least 19 nucleotides of the second strand are complementary to a target RNA sequence; and the first strand includes a terminal cap moiety at the 5'-end ***and*** the 3'-end of said first strand ***and*** the second strand includes a terminal cap moiety at the 3'-end of said second strand, wherein said 3'-end terminal cap moiety is independently selected from the group consisting of 4',5'-methylene nucleotide; 1-(beta-D-erythrofuranosyl) nucleotide, 4'-thio nucleotide; 1,5-anhydrohexitol nucleotide; L-nucleotides; *threo*-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moiety; 3'-3'-inverted abasic moiety; 3'-2'-inverted nucleotide moiety; 3'-2'-inverted abasic moiety; and said 5'-end cap moiety is selected from the group consisting of 4',5'-methylene nucleotide; 1-(beta-D-erythrofuranosyl) nucleotide; 4'-thio nucleotide, 1,5-anhydrohexitol nucleotide; L-nucleotide; LNA; *threo*-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; 3,4-dihydroxybutyl nucleotide; 3,5-dihydroxypentyl nucleotide, 5'-5'-inverted nucleotide moiety; and 5'-5'-inverted abasic moiety (emphasis added). Support for the amendments can be found, inter alia, at page 3, e.g., paragraph [0014]; page 4, e.g., paragraph [0016]; page 5, e.g. paragraphs [0030] and [0035]; page 10, e.g. paragraph [0028]; page 12, e.g. paragraph [0093]; page 14, e.g. paragraphs [0105]-[0109]; pages15-20' page 70, paragraphs [0604]-[0606]; Figure 22, and thoughout the application. Claims 19, 20 and 28-38 have also been amended to replace the term "siNA" with the term "double stranded nucleic acid". Support for the amendment can be found inter alia, at page 3, e.g. paragraph [0013] and throughout the application. Claims 1-17 were previously withdrawn.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the

patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

1. Claim Objections

Claim 24 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 23. Claim 24 has been canceled, thus rendering the objection moot.

2. Claim Rejections under 35 U.S.C. § 112

Claims 19-38 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the term "claim" is missing. Claims 21-27 have been canceled, so the rejection is moot with regard to this claim. Dependent claims 19, 20 and 28-38 have been amended to include the term "claim" with regard to their respective dependency, thus obviating the rejection. In view of all the foregoing, the applicants respectfully request reconsideration and withdrawal of this rejection.

3. Rejection of claims 18-38 under 35 U.S.C. § 102

The Office Action alleged that the instant application was entitled to an effective filing date of PCT/US03/05346, which is February 20, 2003 because the claimed range of 19-29 nucleotides is not disclosed in the earlier documents. The applicants respectfully traverse. In the interest of advancing prosecution, claim 18 has been amended to recite a chemically synthesized double stranded nucleic acid molecule, wherein the double stranded nucleic acid comprises a first strand and a second strand; the first strand comprises a sense region and the second strand comprises an antisense region; each strand is about 18 to about 27 nucleotides in length, about 18 to about 23 nucleotides of each strand are complementary to each other, and at least 19 nucleotides of the second strand are complementary to a target RNA sequence; and the first strand includes a terminal cap moiety at the 5'-end ***and*** the 3'-end of said first strand ***and*** the second strand includes a terminal cap moiety at the 3'-end of said second strand, wherein said 3'-end terminal cap moiety is one of the cap moieties recited in a Markush group. The present application claims priority to, *inter alia*, U.S. Provisional patent application 60/358,580, filed

February 20, 2002. The claims presented above all find support in this application, inter alia, at pages 4, 10, 11, 34, and 35.

Claims 18-22, 25, 27, and 29-38 were rejected under 35 U.S.C. 102(b) as being anticipated by Matulic-Adamic *et al.* (US 5,998,203). Claims 21, 22, 25 and 27 have been canceled, so the rejection is moot as applied to these claims. The Applicants respectfully traverse the rejection with respect to claims 18-20 and 29-38. Matulic-Adamic does not describe a double stranded nucleic acid molecule as presently claimed. First, Matulic-Adamic does not describe a double stranded nucleic acid molecule in which each strand is about 18 to about 27 nucleotides in length, about 18 to about 23 nucleotides of each strand are complementary to each other, and at least 19 nucleotides of the second strand are complementary to a target RNA sequence. Second, Matulic-Adamic does not describe a double stranded nucleic acid molecule in which the first strand includes a terminal cap moiety at the 5'-end *and* the 3'-end of the first strand *and* the second strand includes a terminal cap moiety at the 3'-end of the second strand, wherein said 3'-end terminal cap moiety is one of the cap moieties recited in a Markush group. In view of all the foregoing, the applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 18-22, 25, 28, 29, 33, 34, and 38 were rejected under 35 U.S.C. 102(b) as being anticipated by Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001). Claims 21, 22, 25 and 27 have been canceled, so the rejection is moot as applied to these claims. The Applicants respectfully traverse the rejection with respect to claims 18-20, 28, 29, 33, 34, and 38. Elbashir does not describe a double stranded nucleic acid molecule as presently claimed. Specifically, Elbashir does not describe a double stranded nucleic acid molecule in which the first strand includes a terminal cap moiety at the 5'-end *and* the 3'-end of the first strand *and* the second strand includes a terminal cap moiety at the 3'-end of the second strand, wherein said 3'-end terminal cap moiety is one of the cap moieties recited in a Markush group. Elbashir only teaches introduction of two 2'-deoxy nucleotides at the 3'-overhang positions of a double stranded ribonucleic acid molecule. None of the modifications at the 3'-end of the double stranded nucleic acid molecule set forth in the instant claims are disclosed or contemplated by Elbashir. Further, Elbashir does not teach or contemplate the introduction of terminal cap structures at both the 5'- and the 3'-ends of the sense strand of the siRNA molecule. In addition,

Elbashir was published in March of 2001 and was therefore not published one year before the date of application of the present invention (see discussion of priority above). Elbashir is not appropriate 35 U.S.C. 102(b) art. In view of all the foregoing, the applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 18, 20, 21, 28, 29, 35, 36 and 38 were rejected under 35 U.S.C. 102(b) as being anticipated by Parrish *et al.* (Molecular Cell, Vol 6, pages 1077-1087, 2000). Claim 21 has been canceled, so the rejection is moot as applied to this claim. The Applicants respectfully traverse the rejection with respect to claims 18, 20, 28, 29, 35, 36, and 38. Parrish does not describe a double stranded nucleic acid molecule as presently claimed. Specifically, Parrish does not describe a double stranded nucleic acid molecule in which the first strand includes a terminal cap moiety at the 5'-end *and* the 3'-end of the first strand *and* the second strand includes a terminal cap moiety at the 3'-end of the second strand, wherein said 3'-end terminal cap moiety is one of the cap moieties recited in a Markush group. Parrish only teaches modification in one strand of a duplex, not both strands as is presently claimed. Moreover, none of the modifications at the 3'-end of the double stranded nucleic acid molecule set forth in the instant claims are disclosed or contemplated by Parrish. Further, Parrish does not teach or contemplate the introduction of terminal cap structures at both the 5'- and the 3'-ends of the sense strand of the siRNA molecule. In view of all the foregoing, the applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 18-22 and 25-38 were rejected under 35 U.S.C. 102(b) as being anticipated by McSwiggen (US 2004/0019001). The Applicants respectfully traverse the rejection. McSwiggen was published on January 29, 2004 and was therefore not published one year before the date of application of the present invention (see discussion of priority above). McSwiggen is not appropriate 35 U.S.C. 102(b) art. In view of all the foregoing, the applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 18, 20-22, 25, 27-29, and 33-38 were rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Tuschl et al. (WO 02/44321). Claims 21, 22, 25 and 27 have been canceled, so the rejection is moot as applied to these claims. The Applicants respectfully traverse the rejection with respect to claims 18, 20, 28, 29, and 33-38. Tuschl, which is essentially the same teaching as Elbashir, does not describe a double stranded nucleic acid molecule as presently

claimed. Specifically, Tuschl does not describe a double stranded nucleic acid molecule in which the first strand includes a terminal cap moiety at the 5'-end *and* the 3'-end of the first strand *and* the second strand includes a terminal cap moiety at the 3'-end of the second strand, wherein said 3'-end terminal cap moiety is one of the cap moieties recited in a Markush group. As in the case of Elbashir, Tuschl only teaches introduction of two 2'-deoxy nucleotides at the 3'-overhang positions of a double stranded ribonucleic acid molecule. None of the modifications at the 3'-end of the double stranded nucleic acid molecule set forth in the instant claims are disclosed or contemplated by Tuschl. Further, Tuschl does not teach or contemplate the introduction of terminal cap structures at both the 5'- and the 3'-ends of the sense strand of the siRNA molecule.. In view of all the foregoing, the applicants respectfully request reconsideration and withdrawal of this rejection.

4. Rejection of claims 18-38 under 35 U.S.C. § 103(a)

Claims 49-51, 58, 59, 64, 65, 68-76, and 78-81 were rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), in view of Parrish *et al.* (Molecular Cell, Vol. 6, pages 1077-1087, 2000), Cook *et al.* (US 5,587,471), Wengel *et al.* (WO 99/14226), and Morrissey *et al.* (US 2003/0206887). For the following reasons, the applicants respectfully traverse.

It should be noted from the outset that Morrissey *et al.* is improper 102(e) art that cannot be used under 35 U.S.C. 103(a) because of common inventorship and/or a common obligation of assignment with the instant application. The subject matter of Morrissey *et al.* and the claimed invention were, at the time the claimed invention was made, owned by or subject to an obligation of assignment to Ribozyme Pharmaceuticals, Inc., or its successor in interest, Sirna Therapeutics, Inc.

On this basis alone, this present rejection is improper. Accordingly, its reconsideration and withdrawal is respectfully requested.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success.

Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP §2143.

Here, the knowledge of one of ordinary skill prevented the inventions claimed in the instant application from being realized. There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. There must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required. That knowledge cannot come from the applicants' disclosure of the invention itself. *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315,1318 (Fed. Cir. 1988); *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985).

An examiner can satisfy the burden required for obviousness in light of combination "only by showing some objective teaching [leading to the combination]." *See, In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). Evidence of the teaching or suggestion is "essential" to avoid hindsight. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir.1988). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985). "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998). The need for specificity is important. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed").

Elbashir describes double stranded RNA molecules having 2-4 deoxynucleotides at the 3'-ends of double stranded RNA molecules. Morrissey, as described above, is not prior art to the instant application. Cook teaches various conjugates and modifications that can be incorporated

into single-stranded antisense oligodeoxynucleotides to improve the pharmacokinetic properties of single-stranded antisense oligonucleotides, including glycerty. Wengel teaches LNAs in the context of single-stranded antisense oligodeoxynucleotides, ribozymes, aptamers, and diagnostic probes. None of these cited references either individually or in combination make obvious the claimed invention.

The Office Action states that "It would have been obvious to one of ordinary skill in the art to incorporate glyceryl moieties, LNA moieties, polynucleotide or non-nucleotide linkers, or 2'-deoxy-2'fluoro pyrimidine nucleotides, as taught by Cook et al., Wengel et al., Morrissey et al., and Parrish et al., respectively, into the siRNA molecules taught by Elbashir et al." (Office Action page 16). The Examiner's position goes no further than suggesting that at best it would have been obvious to try the chemical modifications previously used in connection with ribozyme and antisense art. Without acquiescing to that position, even if it were true, it is not the correct standard for judging non-obviousness. Moreover, the subsequent prior art establishes that such suggestions failed in relation to siRNA technology, and this was the status of understanding in the art as of the time of the present invention.

One of skill in the art would not be motivated to combine the cited references to arrive at the presently claimed invention. Elbashir and Tuschl (which contain essentially same content as Elbashir, and the authors of Elbashir are also inventors on Tuschl) are the only references cited that teach a structure having any similarity to the claimed nucleic acid molecules, *i.e.*, a short double stranded RNA molecule having one strand complementary to a target RNA and another strand having sequence comprising a portion of the target RNA sequence. The other references teach antisense and/or ribozyme art. Although antisense and ribozymes are nucleic acid based technologies, they differ substantially from the present invention both mechanistically and structurally in relation to the chemical modification strategies that allow such molecules to remain active. Just as antisense modifications are not amenable to ribozymes and vice versa, neither of these nucleic acid technologies provides any insight or guidance into chemical modification of the siRNAs described by Elbashir and Tuschl. The office action asserts that "One would expect for such modifications to benefit siRNA duplexes, as each had shown to benefit other oligonucleotides such as antisense oligonucleotides." (Office Action page 17). However, this reasoning is flawed because siRNA, antisense and ribozymes are not commonly modified. For example, Elbashir and Tuschl attempted to apply chemical modifications to

siRNA based on the teachings of the prior art, but failed beyond replacing 3'-terminal ribonucleotides with deoxynucleotides (*see*, Elbashir and Tuschl). These molecules were found to have significantly diminished activity or were totally inactive in inducing target specific cleavage by RNAi. For example, the discussion of pages 6881 and 6882 of Elbashir (also in Tuschl, page 46) describes 2'-deoxy and 2'-O-methyl modified siRNA duplexes and is reproduced below:

> To assess the importance of the siRNA ribose residues for RNAi, duplexes with 21 nt siRNAs and 2 nt 3'-overhangs with 2'-deoxy- or 2'-O-methyl-modified strands were examined (Figure 4). Substitution of the 2 nt 3'-overhangs by 2'-deoxynucleotides had no effect and even the replacement of two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Thus, 8 out of 42 nt of the siRNA duplex were replaced by DNA residues without loss of activity. Complete substitution of one or both siRNA strands by 2'-deoxy residues, however, abolished RNAi, as did complete substitution by 2'-O-methyl residues.

Figure 4 of Elbashir (same as Figure 14 in Tuschl) clearly shows that only limited 2'-deoxy substitutions at the 3'-end of a siRNA molecule could be tolerated. Importantly, in all cases where 5'-end substitutions were used, such modifications were shown not to be tolerated for RNAi. In addition, according to "*The siRNA Users Guide*" on page 6885 of Elbashir (Tuschl Pages 49-50),

> 2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.

Based on the teachings of "[t]he siRNA Users Guide" from Elbashir and Tuschl, for example, one of skill in the art would not be motivated to make any modifications beyond the 2'-deoxynucleotide substitutions at the 3'-end of the siRNA molecule and certainly would not be motivated to pursue the presently claimed invention. This is evident from the publications in the field around 2001 and 2002, where experts in the field followed the teachings of Elbashir and designed siRNAs without any modifications other than two deoxythymidine nucleotides at the 3'-end of the siRNA (*see, e.g.,* Bitko *et al.,* 2001, BMC Microbiology, 1, 34 page 9, left column under heading Materials and Methods section; Kumar *et al.*, 2002, Malaria Journal, 1:5, page 9, right column, under heading Transfection by Inhibitory dsRNA"; Holen *et al.,* 2002, Nucleic

Acids Research, 30, 1757-1766, Figures 1, 2 and 6). These prior art references demonstrate that Elbashir and Tuschl taught away from the presently claimed invention

Further, a plain reading of Elbashir and Tuschl teach that modifications beyond the use of deoxynucleotides at the 3'-terminus of siRNAs are not tolerated and likely interfere with protein associated with siRNP assembly. As such, Elbashir and Tuschl provide no motivation to a person skilled in the art to take the teachings of antisense and ribozymes and apply it to double stranded RNA molecules as presently claimed because Elbashir and Tuschl tried this approach and failed. Elbashir and Tuschl therefore teach away from using modifications beyond use of 2'-deoxynucleotides at the 2-4 3'-terminal positions of the double stranded RNA molecules. One of skill in the art would not be motivated to incorporate modifications at the 5' and 3'-end of the sense strand and at the 3'-end of the antisense strand of the double stranded RNA molecules as presently claimed and expect such siRNA molecules to be active to mediate RNA interference. As stated in Elbashir and Tuschl, end modification of siRNA other than deoxynucleotide substitution of the 2-4 nucleotides at the 3'-end of the siRNA, are not tolerated because such modifications at the 3'-end and 5'-end allegedly interfere with protein associated with siRNP assembly. Based on this teaching alone, one skilled in the art would be dissuaded from making any terminal modifications at the 5' and/or 3' ends of the siRNA molecules. Therefore introduction of cap structures at the 5'-end and 3'-end of the first strand and at the 3' end of the second strand of an double stranded nucleic acid molecule as set forth in the instant claims would not be obvious.

The applicants have shown that 5' and 3'-end sense strand and at the 3'-end antisense strand modifications are well tolerated in double stranded nucleic acid molecules targeting gene expression, as evidenced by the fact that the applicants were the first to utilize double stranded nucleic acid molecules as presently claimed to successfully target gene expression. For example, in the present application, applicant has designed, synthesized, and tested the claimed modified double stranded nucleic acid molecules having potent activity directed against various targets, (see for example Figures 29-41 with a corresponding description on pages 35, paragraph [0283] to page 36, paragraph [0295]). The present application (as well as with many others subsequently published) demonstrates that application of 5' and 3' sense strand and 3'-end antisense strand modifications to double stranded nucleic acid structures are well tolerated for maintaining potent RNAi activity against target nucleic acid sequences. Therefore, a person skilled in the art would

not have been motivated to follow the teachings of Elbashir or Tuschl, let alone the antisense or ribozyme art to make and use the double stranded nucleic acid molecules of the present invention.

Moreover, the cited references, alone or in combination, do not provide a reasonable expectation of success. The existence or lack of a reasonable expectation of success is assessed from the perspective of a person of ordinary skill in the art at the time the invention was made (see discussion of priority above). *See, Micro Chem. Inc. v. Great Plains Chem. Co.,* 103 F.3d 1538, 1547, 41 U.S.P.Q.2d 1236, 1245 (Fed. Cir. 1997). The inventors' ultimate success is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. *See, Standard Oil Co. v. American Cyanamid Co*, 774 F.2d 448, 454, 227 U.S.P.Q. 293, 297 (Fed. Cir. 1985). It is impermissible to use hindsight. That is, using the inventors' success as evidence that the success would have been expected. *See, In re Kotzab*, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313, 1316, (Fed. Cir. 2000). For example, the office asserts that "One would expect for such modifications to benefit siRNA duplexes, as each had shown to benefit other oligonucleotides such as antisense oligonucleotides." (Office Action page 17). However, this fact was not known until well after the date of the claimed invention, *i.e.*, that 5' and 3'-end sense strand modifications together with 3'-end antisense strand modifications are tolerated in short double stranded nucleic acid molecules as presently claimed and as described in the applicant's own work.

The foregoing argument as to why the combination of cited references do not render the present claims obvious is further substantiated by the enclosed Declaration under 37 C.F.R. 1.132 of inventor James McSwiggen. In his Declaration, Dr. McSwiggen explains why those working in the RNAi field at the time of the present invention would not be motivated by the teachings of the antisense and ribozyme arts to make the modifications recited in the present claims, nor would they have a reasonable expectation of successfully applying those teachings to obtain the presently claimed invention.

As Dr. McSwiggen explains, there are significant structural differences between antisense oligonucleotides and ribozymes on the one hand and siRNAs on the other. Studies had shown that enhancing stability of antisense oligonucleotides and ribozymes was critical to achieving optimal activity. The relatively high potency of siRNAs, however, suggested that no additional

stability-inducing modifications would be necessary. Furthermore, it was common knowledge that single stranded nucleic acids were more susceptible to nuclease attack compared to double stranded nucleic acids such as siRNAs. Dr. McSwiggen also notes that teachings within the RNAi art (specifically Elbashir *et al.* 2002 Methods 26:199-213) explicitly taught a desired protocol for siRNA synthesis in which only the terminal TT was modified (as dTdT). For these reasons, Dr. McSwiggen explains, the antisense art and ribozyme art would not supply those skilled in the art with a suggestion or motivation to modify siRNAs in a manner similar to modifications made to antisense oligonucleotides and ribozymes.

Dr. McSwiggen further explains that the art provided no guidance as to the sorts of modifications of siRNA that would lead to the presently claimed invention. (*See,* paragraphs 12 *et seq.*) Dr. McSwiggen describes several critical structural and functional distinctions between antisense oligonucleotides and ribozymes on the one hand and siRNAs on the other and explains why one of ordinary skill in the RNAi field would not apply the teachings from the antisense and ribozyme arts to siRNAs.

Dr. McSwiggen also explains that the most relevant art at the time, that is, art dealing directly with modified siRNAs, provided data and other teachings suggesting that extensive modifications of siRNAs were undesirable, discouraging the present inventors and likely steering others in the field away from exploring chemical modifications of siRNAs beyond replacing the 3′-terminal positions.

Based on the foregoing, Dr. McSwiggen concludes that at the time of the present invention those skilled in the art would not be motivated to apply, in particular, 4',5'-methylene nucleotides, 1-(beta-D-erythrofuranosyl) nucleotides, 4'-thio nucleotides, 1,5-anhydrohexitol nucleotides, L-nucleotides, LNAs, *threo*-pentofuranosyl nucleotides, acyclic 3',4'-seco nucleotides, acyclic 3,4-dihydroxybutyl nucleotides, acyclic 3,5-dihydroxypentyl nucleotides, inverted nucleotides, and inverted abasic moieties (among others) to siRNAs merely because such modifications were used to stabilize antisense and ribozymes. Indeed, Dr. McSwiggen notes, the RNAi literature demonstrated that knowledge derived from antisense and ribozymes regarding stabilization could not be readily applied to siRNAs. And, Dr. McSwiggen further attests, because the mechanism of action between antisense and ribozymes on the one hand and siRNAs on the other differed so significantly, those skilled in the art would have believed, as the

present inventors discovered, that teachings from the antisense and ribozyme arts could not be directly applied to siRNAs.

For the reasons set forth above, Elbashir, in view of Parrish, Cook, Wengel, and Morrissey do not teach or suggest making the chemically synthesized double stranded nucleic acid molecule as presently claimed, nor imbue the ordinary artisan with a reasonable expectation of success. Therefore, the cited references do not render the present invention obvious. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection.

5. Obviousness-type Double Patenting

The Office rejected claims 18-24 and 28-38 for obviousness type double patenting over claims 1-6, 9-19, 22 and 31 of copending Application No. 10/877,889 and claims 1-6, 9-19, 22 and 31 of copending Application No 10/918,987. Although the applicants traverse these rejections, solely in an effort to advance prosecution they submit herewith terminal disclaimers over the subject applications.

In view of all the foregoing, the applicants respectfully request reconsideration and withdrawal of this rejection.

If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully submitted,

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